Review Article

Clinical Utility and Measurement of Procalcitonin

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Abstract

Procalcitonin (PCT), regarded as a biomarker specific for bacterial infections, is used in a variety of clinical settings including primary care, emergency department and intensive care. PCT measurement aids in the diagnosis of sepsis and to guide and monitor antibiotic therapy. This article gives a brief overview of PCT and its use in guiding antibiotic therapy in various clinical settings, as well as its limitations. PCT performance in comparison with other biomarkers of infection in particular CRP is also reviewed. Owing to its greater availability, CRP has been widely used as a biomarker of infection and sepsis. PCT is often reported to be more superior to CRP, being more specific for sepsis and bacterial infection. PCT starts to rise earlier and returns to normal concentration more rapidly than CRP, allowing for an earlier diagnosis and better monitoring of disease progression.

Introduction

PCT, the precursor of the hormone calcitonin, has been used as a biomarker to aid in diagnosis of bacterial infection or sepsis, as well as in differentiating bacterial pneumonia from viral pneumonia and chronic obstructive pulmonary disease (COPD).[1-3] Diagnosis of sepsis is especially challenging as the clinical criteria for its diagnosis overlap with non-infective causes of systemic inflammation. Early diagnosis allows for timely therapeutic measures to be initiated, whilst delay leads to sepsis-related morbidity and mortality.[4] The emergence of antibiotic resistance, on the other hand, calls for a more stringent effort to reduce antibiotic overuse. This is especially true for acute respiratory tract infections where antibiotics are prescribed often despite the majority of infections being caused by viruses rather than bacteria.[5-6] There is growing evidence for the use of PCT guided antibiotic therapy, both for initiation and for discontinuation of antibiotics. Clinical algorithms with specific PCT cut-offs in various clinical settings and patient populations are used as part of the antibiotic stewardship program. Most compelling evidence for PCT use is in adults with respiratory tract infections and in the critically ill, where randomised controlled trials (RCT) have demonstrated the safety and efficacy of PCT guided antibiotic therapy. For other types of infections, the evidence for the use of PCT measurement is limited to observational studies, with its safety and benefit remaining undefined.[7]

Biochemistry and Physiology of PCT

PCT is a 116-amino acid peptide with a molecular weight of 14.5 kDa. It consists of three sections; the amino terminus (57 amino acids), immature calcitonin (33 amino acids) and calcitonin carboxyl-terminus peptide 1 (CCP-1) also known as katacalcin (21 amino acids) (Figure 1).[8] Its production is governed by the calcitonin 1 gene (CALC-1) on chromosome 11. The product of this gene, prePCT, undergoes proteolytic cleavage producing PCT, which is further processed to the mature calcitonin molecule. Transcription and translation of CALC-1 gene is normally confined to the thyroid C-cells and, to a lesser extent other neuroendocrine cells. Production is, however, activated in all parenchymal tissues in response to bacterial infection, mediated by cytokines interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α) and interleukin-1β (IL-β).[8] These other tissues lack the ability to cleave PCT to its mature form, calcitonin, leading to accumulation of PCT.[9] Conversely, PCT production is attenuated by interferon-γ primarily secreted in response to viral infection.[10] This characteristic makes PCT a more specific marker for bacterial infection.

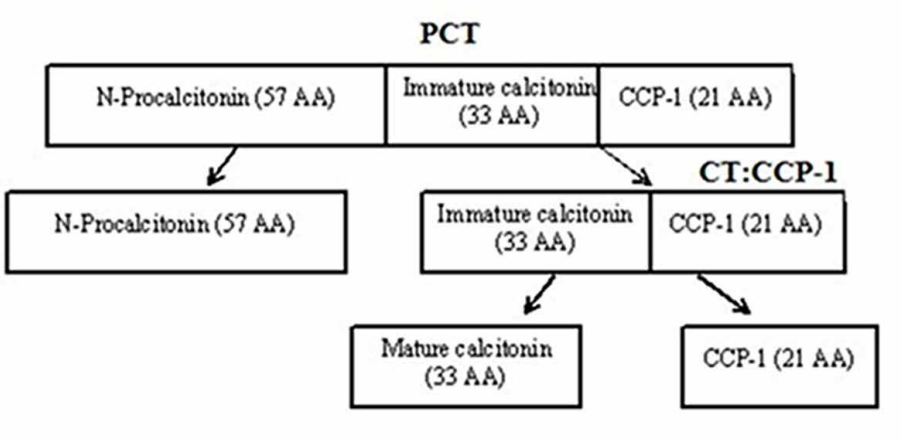

Figure 1. Schematic diagram of PCT molecule and of its constituent peptide. Commercially available PCT assays recognise PCT and CT:CCP-1 forms. Adapted from Schneider and Lam 2007.[11]

Serum PCT concentration in healthy individuals is typically <0.1 μg/L.[12] In the presence of bacterial infection, PCT increases, and the degree of rise correlates with the severity of the infection. Patients with localised infection have smaller increases of PCT in comparison to those with generalised sepsis, severe sepsis and septic shock. A declining concentration usually reflects resolution of disease. Table 1 shows the upper reference limit and the interpretation of PCT concentration based on disease severity specific cut-offs. Importantly, interpretation must be based on patient's clinical context as other factors may also cause an increase or decrease PCT (see later). PCT is detectable 3 to 4 h following an infection, following the release of TNF-α at 90 minutes and IL-6 at 3 h. It peaks at 6 to 12 h and has a half-life of about 24 h. This favourable kinetic profile, and its specificity and sensitivity for bacterial infection make it suitable for diagnosis and disease progression monitoring.

Other Causes of Increase or Decrease in PCT

Factors which may cause a raised PCT apart from a bacterial infection include recent major surgery,[14] severe trauma,[15] severe burns[16] and prolonged cardiogenic shock.[17] However, in the absence of infection, these patients should have decreasing PCT levels on subsequent measurements. Other infections which can activate the release of cytokines include fungal[18] and malarial infections.[19] Patients on medications which stimulate cytokine release such as OKT3, antilymphocyte globulins, alemtuzumab, IL-2 and granulocyte transfusion will also have an elevated PCT level.[20] Dysregulated PCT production leading to a high PCT is seen in patients with paraneoplastic syndromes due to medullary thyroid and small cell lung carcinomas.[21]

Newborns have been observed to have a baseline PCT that is higher than seen in adults. PCT increases further over the first 24 h after birth and stays elevated during the first 2 days of life.[22] Figure 2a shows the age specific 95% reference interval

Table 1. Interpretation of PCT concentration. Adapted from Meisner M.[13]

PCT (μg/L)	Interpretation
< 0.05	Healthy adult
0.05 – <0.5	Systemic infection is unlikely although localised infection is possible
0.5 – <2	Systemic infection is possible but other conditions (e.g. major trauma, recent surgery, severe cardiogenic shock) may also induce significant PCT rises.
2 – <10	Systemic infection is likely
≥ 10	High likelihood of severe bacterial sepsis or septic shock

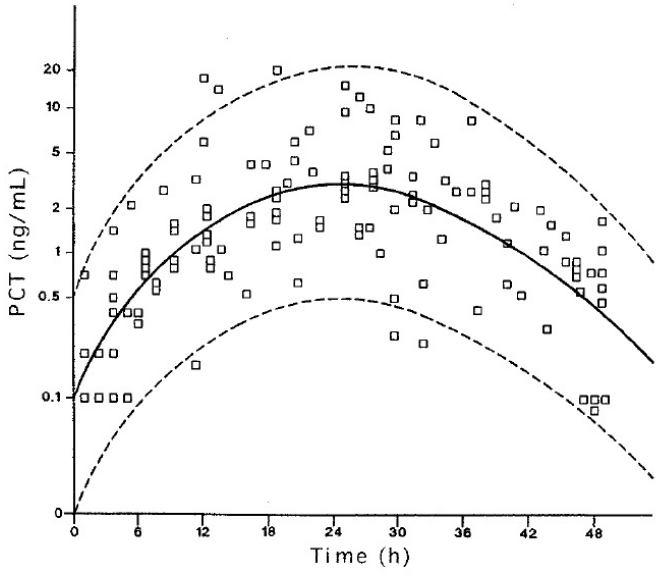

Figure 2a

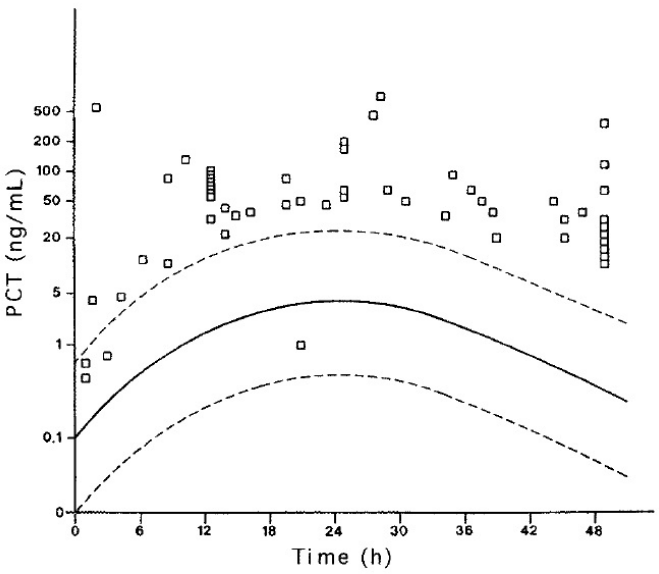

Figure 2b

Figure 2a. Age specific 95% reference range for PCT in healthy neonates.

Figure 2b. PCT values obtained for patients with early onset infection within 48 h of age.

The squares represent single values; dotted lines represent lower and upper limits of reference range, the bold represents the geometric mean.

Reproduced from Cheisa C, Reliability of procalcitonin concentrations for the diagnosis of sepsis in critically ill neonates, Clin Infect Dis, 1998;26:664-72, by permission of Oxford University Press.

for PCT in healthy neonates during the first 48 h of life.[23] PCT was shown to be significantly higher in newborns with infections than those without (Figure 2b).[23] Thus, PCT may be used for early diagnosis of sepsis in this age group also.

Higher than normal baseline PCT levels are seen in patients with chronic kidney disease (CKD) regardless of whether they are on renal replacement therapy (RRT) or not.[24,25] In the absence of infection, roughly 36% of CKD patients who are dialysis naive have PCT levels ≥0.5 µg/L, whilst in the presence of infection, 36-100% would have a PCT ≥0.5 µg/L.[26] The baseline PCT in patients with CKD stage 5 who are not on RRT averages between 0.1-1.8 µg/L.[26] The pathophysiology of elevated PCT in these patients is thought to be an increase in pro-inflammatory mediators stimulating the immune system causing inflammation and hence release of PCT into the circulation.[27] Of interest, the rate of decline in plasma PCT following resolution of infection has been shown not to differ in patients with severe CKD compared with subjects with normal renal function.[25]

PCT levels were shown to decrease significantly following the start of RRT.[27] The magnitude of decrease varies depending on the type of RRT. The highest decrease is seen in patients on high flux haemodialysis (HD) compared to those on peritoneal dialysis (PD) and continuous venous-venous haemodialysis (CVVHD).[26] Following high flux HD, a decrease of 21 to 83% is seen. PCT will increase gradually over 48 h following the end of RRT, thus, returning to baseline prior to the next dialysis session. In patients on CVVHD with systemic infection, a significant decrease is seen within 15 minutes of starting CVVHD and may continue to decrease for up to 12-24 h after starting CVVHD; therefore, it is recommended that PCT be determined prior to starting CVVHD.[26]

A low or normal PCT does not always indicate the absence of bacterial infection. This may especially be the case in the early course of a bacterial infection, in localised infections (e.g. empyema, osteomyelitis) or in subacute infective endocarditis.

Analytical Artefacts

A hook effect may occur with extremely high PCT concentrations, resulting in a much lower reported value. It was reported in a patient specimen with PCT of 10,270 µg/L (calcitonin 313,600 pg/mL).[28] When measured without dilution, the PCT was 2.8 µg/L. Heterophilic antibodies may theoretically lead to an erroneous PCT result although no case example could be found in the literature.

PCT Assay

All currently available assays for quantification of PCT are based on immunoassay techniques. The first commercially available PCT assay was the BRAHMS PCT LIA® (Thermo Fisher, Hennigsdorf, Germany), a manual luminometric immunoassay. A more sensitive and rapid automated assay known as the BRAHMS PCT Kryptor®) (Thermo Fisher, Hennigsdorf, Germany) was then developed, the first to be cleared by FDA in 2008 for use in diagnosis of severe sepsis and septic shock.[13] Following this, several diagnostic companies have partnered with BRAHMS to develop PCT assay on their individual platforms, with minor differences in their analytical characteristics (functional sensitivity, measuring range, etc.) and technologies (i.e. immunoluminometric, enzyme-linked immunofluorescent, chemiluminescent, electrochemiluminescent). A latex-enhanced immunoturbidimetric assay developed by Diazyme Laboratories, USA now allows PCT to be measured on a vast array of clinical chemistry analysers. With no reference method and a lack of reference material, questions have been raised as to whether the clinical cut-offs used in generally used algorithms would apply to other PCT assays. In a multicentre study in 2015, Dipalo and co-workers compared results of BRAHMS PCT Kryptor with four PCT immunoassays (DiaSorin Liaison, Vidas, Roche E601 and Siemens Advia Centaur), and Diazyme immunoturbidimetric assay (on Abbott Architect c16000, Siemens Advia 2400, Roche Cobas C501 and Beckman Coulter AU5800).[29] Statistically significant differences in results were observed on Vidas, Advia Centaur, Architect, Cobas C501 and AU5800 when compared to BRAHMS PCT Kryptor. Nevertheless, satisfactory correlation coefficients (r = 0.899 and 0.988) were obtained. The mean bias for all methods except for Vidas was less than ±1.02 µg/L. Importantly, at the three relevant PCT diagnostic thresholds for bacterial infections, the agreement between BRAHMS PCT Kryptor with the other methods and reagents evaluated in this study was optimum: 83–98% at 0.50 µg/L, 90–97% at 2.0 µg/L, and 98% at 10 µg/L. It was concluded that all the assays evaluated were aligned with the BRAHMS PCT Kryptor and that the same clinical PCT cut-offs may be used. The bias that exists between the methods nevertheless indicates that a single method should be used for patient monitoring. Serial PCT measurement rather than a single measurement is advisable in most situations. It goes without saying that the PCT result should be used in conjunction with clinical evaluation of the patient and not on its own.

A point of care test for PCT (BRAHMS PCT-Q) is available, which is a test strip using immunochromatographic technique. A coloured band appears 30 minutes after application of 200 µL serum or plasma with the intensity of the band read against a reference card. The results are reported as <0.5, 0.5–2.0, 2.0–10 and >10 µg/L.[30] The semi quantitative nature of the results however may limit its clinical use where a change in the PCT trend is important to monitor the patient's clinical status.[7] It may still be valuable in cases where quantitative measurements are not available within a reasonable period of time (1- 3 h).[31]

Indication for PCT Use

The main indication for PCT measurement is to aid in the diagnosis of bacterial infection and as a marker to guide antibiotic therapy. Several studies have investigated the use of PCT for initiation, discontinuation and escalation of antibiotics use based on specific algorithms. The algorithms for PCT guided antibiotic therapies were derived from several observational and prospective studies and were validated in a randomised controlled trial (RCT). Specific PCT cut-offs were proposed depending on the probability of bacterial infection in certain groups of patients and clinical situations, e.g. primary care, emergency department (ED) and intensive care unit (ICU). In general, in patients with a lower probability of bacterial infection as is seen in primary care and ED, the following cut-offs are used; antibiotics are discouraged if PCT is <0.1 µg/L (bacterial infection very unlikely) or 0.1 – 0.25 µg/L (bacterial infection unlikely) and encouraged if PCT is >0.25-0.5 µg/L (bacterial infection likely) or >0.5 µg/L (bacterial infection very likely). Higher PCT cut-off values are used for ICU patients. Some of the evidence for the use of PCT in these three clinical settings will be reviewed. Timely diagnosis and use of antibiotics is an effective measure for reducing morbidity and mortality, whilst minimising the risk of emergence of antibiotic resistance and adverse events.

Primary Care

Two RCTs have examined PCT guided antibiotic therapy in patients with acute respiratory tract infections using similar PCT cut-offs as described above. In 2008, Briel and co-workers measured PCT at presentation, and if antibiotics were withheld, a second PCT measurement was measured at day 3.[3] They found an overall 72% reduction in antibiotic prescription rate and an average of a day's reduction in antibiotic duration for those in the PCT guided antibiotic therapy group compared to the standard care group. The main reduction in antibiotic prescription rate was seen in those with a diagnosis of upper respiratory tract infection (URTI), asthma or acute bronchitis (~80%) whilst about 40% reduction was seen in those with acute exacerbation of COPD and pneumonia. In 2010, Burkhardt and co-workers suggested a simpler protocol using a single PCT measurement at presentation, making it more feasible for use in primary care with instructions for antibiotic treatment if PCT was >0.25 µg/L and no antibiotic if PCT was <0.25 µg/L.[32] A 42% reduction in antibiotic exposure was

achieved. In both trials, no differences were observed in terms of primary safety end points between the PCT group and controls for up to 28 days. The PCT group did not have more complications in terms of infection relapse and days off work but fewer antibiotic side effects were observed. The mortality rates in both trials were similarly low.

ED

The ProHosp study was a multicentre RCT in a hospital setting of adult patients presenting with lower respiratory tract infection (LRTI), which ranged from the self-limiting acute bronchitis to severe acute exacerbation of COPD, and community acquired pneumonia (CAP).[33] Decisions to initiate and to stop antibiotics were made using the above pre-specified PCT cut-offs. Patients in the PCT guided group had PCT measured at presentation and, if antibiotic was started, PCT measurements were repeated at days 3, 5 and 7. In those in whom antibiotics were withheld, PCT was repeated after 6 to 24 h. Overruling of the algorithm was allowed for respiratory or haemodynamic instability and positive antigen test for Legionella pneumophilia or in patients with severe CAP or COPD. Additionally, in those with a high initial PCT (>10 μg/L), a decrease by >80% was another indication for stopping antibiotics. Compliance with the algorithm was 90%. Exposure to antibiotics was reduced by approximately one third in all diagnostic groups. The greatest reduction was seen for those with COPD and acute bronchitis, due to withholding of antibiotics. Adverse effects and mortality were not significantly different in the two groups.

The algorithm used in the RCT was tested in an observational quality surveillance in the ProReal study which included 1759 consecutive adults with LRTI (53.7% CAP, 17.1% acute exacerbation of COPD and 14.4% bronchitis) presenting to ED or outpatients department in 14 centres in Switzerland, France and United States.[34] The aim was to investigate the effectiveness of PCT to guide antibiotic therapy outside of the controlled situation seen in RCTs. The centres varied in terms of familiarity with the PCT algorithm and antibiotic prescription culture. The overall compliance rate with the algorithm was 68.2% with significantly higher compliance seen in out-patients compared to inpatients; those in the algorithm-experienced compared to algorithm-naive centres and in Switzerland and France compared to US centres. The mean overall reduction in hospital stay was approximately 20% (from 7.4 to 5.9 days). Multivariable analysis controlling for severity of illness and other confounders confirmed that neither withholding antibiotics on hospital admission in patients with a low PCT nor discontinuation of antibiotic therapy in patients with an appropriate decrease in PCT was associated with an increased risk of mortality, or of other adverse events during hospitalisation or the next 30 days, confirming the safety of PCT-guided antibiotic stewardship outside study conditions.

ICU

The likelihood of severe infection and sepsis is high in ICU. Several RCTs have determined the usefulness of PCT guided algorithms, as part of antibiotic stewardship programs. One of the largest RCT was the PROcalcitonin to Reduce Antibiotic Treatments in Acutely ill patients (PRORATA) trial, a study of patients with suspected bacterial infection (73% with a respiratory infection source) involving seven ICUs.[35] Two algorithms were used, one to start and another to stop antibiotic therapy. Higher cut-off values were used compared to those in the respiratory trials (Figure 3). The criterion for stopping antibiotics was a decrease of PCT ≥80% from peak value or PCT ≤0.5 μg/L. Adherence to the algorithm was lower than in the respiratory trials with most non-adherences occurring during the first part of the study where patients were started on antibiotics even if the PCT was <0.5 μg/L. The investigators found PCT guided strategy was effective in reducing antibiotic exposure with no apparent adverse outcomes. However, safety concerns were raised because of a slightly higher mortality at day 60 observed in the PCT group with odds ratio for death of 1.09 (0.79-1.51) compared to the control group, even though this was not statistically significant.

The Stop Antibiotics on Procalcitonin guidance Study (SAPS) looked at the algorithm to stop antibiotics only.[36] The study was conducted in a health care setting of a comparatively low use of antibiotics. The PCT guided strategy reduced the duration of antibiotic usage to 5 days compared with 7 days in the standard-of-care group. Furthermore, the mortality at 28 days (19.6%) and 1 year (34.8%) for the PCT guided group were significantly lower ($p<0.05$) compared to the standard-of-care group (25% at 28 days and 40.9% at 1 year).

The Placebo-Controlled Trial of Sodium Selenite and Procalcitonin Guided Antimicrobial Therapy in Severe Sepsis (SISPCT) on the other hand showed that PCT guided antimicrobial therapy was not associated with improved 28 day mortality in patients with severe sepsis.[37] However, there was a significant reduction ($p=0.02$) in antibiotic exposure by 4.5% between the PCT guided group compared to those without PCT guidance group.

In contrast to the use of PCT in initiating and stopping antibiotics, using PCT as biomarker for intensification of antibiotic therapy in adult ICU patients is discouraged as this approach was associated with an increase in morbidity as demonstrated in the Procalcitonin and Survival Study (PASS), a large study involving more than 1000 patients.[38] Those in the

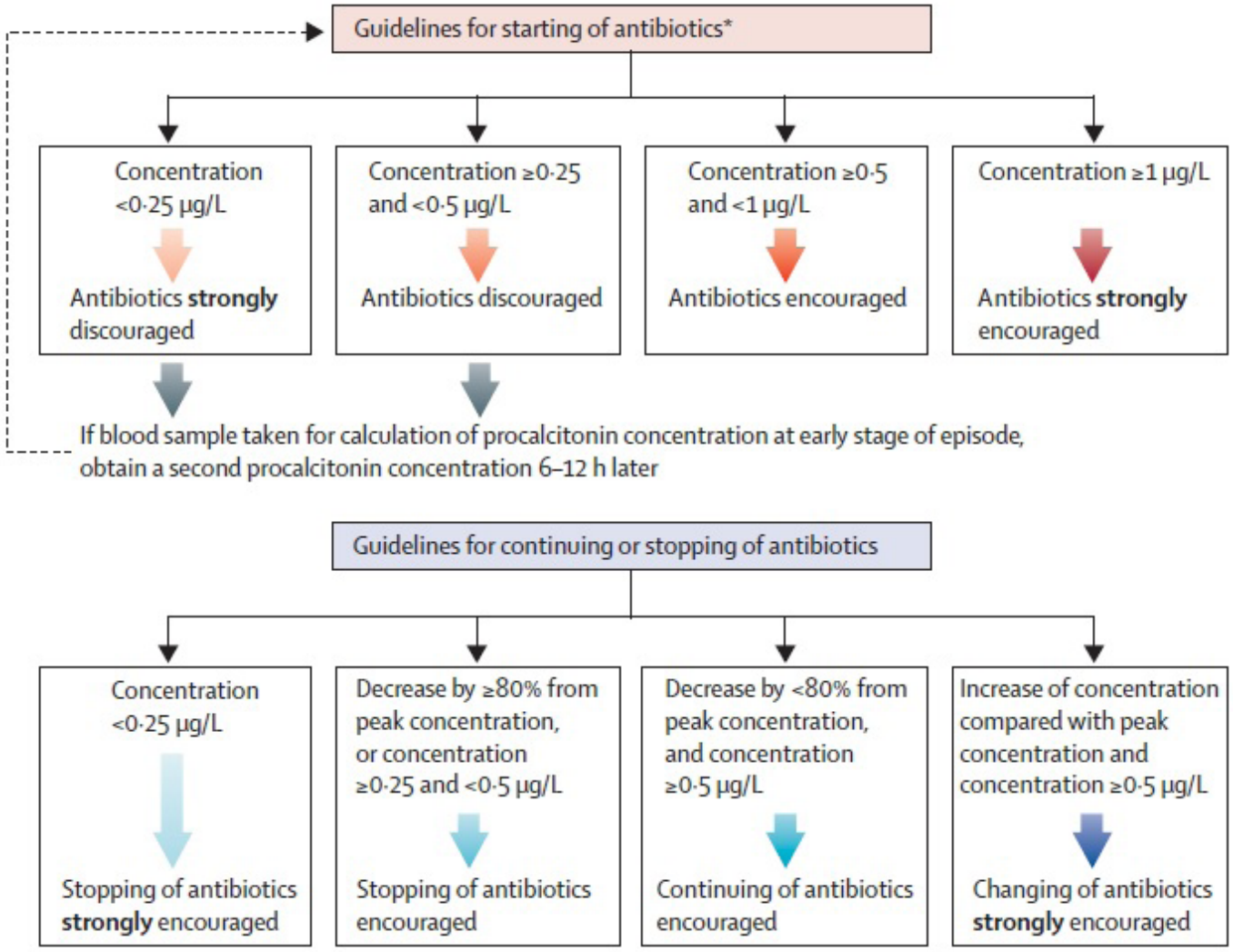

Figure 3. Algorithms for initiating and discontinuing antibiotic therapy in ICU.

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PCT group had serial daily PCT measurements. A PCT of >1 µg/L or a less than 10% decrease from the previous day was taken to indicate an ongoing or uncontrolled infection. These patients were subjected to further investigations including microbial and radiological examinations. A drug-escalation algorithm was followed in addition to the standard-of-care guidelines. Even though the 28 day mortality was comparable between the two groups, the PCT group consumed more antibiotics (a 50% relative increase in duration of antibiotic therapy and a 7.9% absolute increase in the number of days on ≥3 antibiotics), had significantly longer ICU stay and significantly more days on mechanical ventilation, dialysis and vasopressors. It was suggested that the increased morbidity may have resulted from the toxic effects of the medications used in the intervention algorithm on renal and respiratory tissues.[38]

Comparison between PCT and CRP

CRP is a conventional biomarker of infection which is most frequently studied. It is an acute phase protein synthesised by the liver in response to IL-6.[39] Its concentration in blood begins to rise 4 to 6 h following an inflammatory stimulus, doubling every 8 h, and peaks at 36 to 50 h,[40,41] with a half-life of 19 h.[42] Its concentration is also thought not to be affected by RRT,[27] systemic steroids[43] or neutropaenia.[44] The CRP assay is inexpensive, which is particularly useful in centres with limited financial resources. CRP is elevated in patients with community acquired pneumonia compared to healthy controls, and is able to distinguish patients with pneumonia from exacerbation of COPD[45] and heart failure.[46] A decline in CRP is associated with recovery and better prognosis in patients with severe infection. In the primary care setting, using CRP point of care testing to guide antibiotic therapy

reduces prescription rate for lower respiratory tract infections without compromising patient outcome.[47]

Whether PCT is a better marker than CRP would depend on several factors. The potential advantages of PCT over CRP include a more rapid increase and earlier peak at 24 h following infection and a faster decrease following resolution of infection.[8] PCT was found to be more sensitive and specific than CRP for the diagnosis or prognosis of sepsis by some investigators,[48,49] whilst others have found no advantage of PCT over CRP.[50] PCT was suggested to have superior efficacy compared with CRP in predicting bacteraemia in patients with community-acquired pneumonia.[51] Similarly, a case-control study of inpatients with positive and negative cultures showed that the optimal PCT cut-off of 0.5 μg/L was superior to a CRP cut-off 50 mg/L for predicting bacteraemia. The study also demonstrated that PCT was significantly higher in subjects with Gram-negative rod infections than those with Gram-positive coccal infections.[52] In contrast, CRP was found to be a better predictor of response to treatment in exacerbations of COPD.[53] In an observational study, both CRP and PCT independently distinguished pneumonia from acute exacerbations of asthma or COPD, and PCT and CRP were strongly correlated.[45] A CRP >48 mg/L identified patients with pneumonia with a sensitivity and specificity of 91% and 93%, respectively. Therefore, it was suggested that CRP may be useful to guide antibiotic therapy in hospitalised patients with lower respiratory tract infections.

The clinical utility of PCT and CRP in differentiating between confirmed isolated viral pneumonia and mixed (bacterial and viral) pneumonia was assessed during the 2009 H1N1 pandemic.[54] The sensitivity and specificity for detection of mixed bacterial infection pneumonia were 56% and 84% respectively for PCT >1.5 μg/L, and 69% and 63% respectively for CRP >100 mg/L. Using PCT and CRP in combination resulted in a sensitivity and specificity of 50% and 93%, respectively. A combination of a low CRP and a low PCT suggested that pneumonia was unlikely to be caused by mixed bacterial infection. In another study, a PCT <0.8 μg/L suggested that bacterial infection was unlikely in patients with confirmed H1N1 influenza (negative predictive value of 91%).[55]

Whilst algorithms for PCT guided antibiotic therapy have been proved to be useful in reducing duration of antibiotic therapy in several RCT in different clinical settings, very limited testing has been done for CRP-based algorithms in RCTs. In 2013, Oliveira and co-workers performed a RCT comparing CRP and PCT in adult patients admitted to ICU with severe sepsis or septic shock.[50] Decision to discontinue antibiotics was based on PCT or CRP algorithms (Figure 4), clinical response and Sequential Organ Failure Assessment (SOFA) score. In patients in whom infection had clinically resolved, antibiotics were discontinued in both groups regardless of the CRP or PCT level by day 7 at the latest. Furthermore, if patients had initial SOFA score >10 at inclusion, antibiotics were prescribed for at least 7 days, even when discontinuation criteria had been fulfilled. The results showed no significant difference between duration of antibiotic use between the PCT (8.1 days) and CRP (7.2 days) groups. There were also no differences in terms of mortality or morbidity. These results suggest that an algorithm using CRP might be as safe to guide antibiotic discontinuation as that of PCT, but at a reduced cost. However, this premise needs to be confirmed in a larger trial. Interestingly, this study protocol supports the hypothesis that 7 days represents a feasible and safe maximum antibiotic duration of therapy as demonstrated in previous studies of patients with severe infections.[56-59]

Recently, the use of tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) was assessed in combination with CRP and interferon gamma induced protein-10A for distinguishing between bacterial and viral infections in both paediatric and adult patients seen in the hospital.[60] In contrast to PCT, TRAIL is a protein that is up-regulated during viral infections and decreased during bacterial infections. Thus, its use is complementary to markers such as in CRP and PCT

Table 2. CRP- and PCT-guided antibiotic therapies (adapted from Oliveira C, 2013).[50]

	Decision to stop antibiotics*
PCT	PCT < 0.1 μg/L or decrease $\geq 90\%$ from initial value
CRP	CRP < 25 mg/L or decrease $\geq 50\%$ from initial value

*In combination with decreased SOFA score

which are induced by bacteria. A combination of the three biomarkers resulted in an AUC 0.94±0.04 for distinguishing between bacterial and viral infections. A recent publication validated the use of the three biomarkers in combination to differentiate between bacterial and viral infection in young children (2-60 months age) and may potentially reduce antibiotic misuse in these children.[61]

Conclusion

PCT is considered a specific biomarker for bacterial infection and has several benefits. As with any other biomarker, interpretation must be made with reference to patient's clinical context. PCT measurement may help with the decision to initiate antibiotic therapy in low risk acuity of infection. Evidence for PCT-guided antibiotic therapy is strongest for de-escalation of antibiotic therapy in patients with sepsis or high-risk infection. Serial PCT measurement rather than a single measurement is advisable in most situations. Users must be aware of other conditions which may affect PCT levels.

Competing Interests: None declared.

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